



Clinical trial results:

An open-label, non-controlled, multicenter, multinational study to evaluate the efficacy and safety of Zemaira® administration in chronic augmentation and maintenance therapy in subjects with emphysema due to alpha1-proteinase inhibitor deficiency who completed clinical study CE1226_4001

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2007-007129-38
Trial protocol	IE CZ DE FI SE EE DK
Global end of trial date	09 September 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	CE1226_3001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00670007
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Strasse 76, Marburg, Germany, 35041
Public contact	Trial Registration Co-ordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Co-ordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 December 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of Zemaira® on the progression of emphysema, assessed by the decline of lung density, measured by yearly computed tomography (CT).

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, and local legal requirements. The study protocol and all amendments were approved by the Independent Ethics Committee(s)/ Institutional Review Board(s) of the participating centers.

Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Denmark: 35
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Ireland: 19
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Canada: 25
Worldwide total number of subjects	140
EEA total number of subjects	98

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	130
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted at 22 centers in Europe, Canada, and Australia. Alpha1-proteinase inhibitor (A1-PI) deficient individuals with emphysema, who had completed the 2-year treatment and observation periods in study CE1226_4001, except those participating in the USA, were invited to participate in study CE1226_3001.

Pre-assignment

Screening details:

Subjects who had participated in the CE1226_4001 study, met the inclusion and exclusion criteria, and signed the informed consent were included in study CE1226_3001.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Zemaira®
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Zemaira®
Investigational medicinal product code	CE1226
Other name	Alpha1-Proteinase Inhibitor (human)
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The Zemaira® dose was 60 mg/kg body weight, administered intravenously once per week.

Number of subjects in period 1	Zemaira®
Started	140
Completed	131
Not completed	9
Adverse event, serious fatal	1
Consent withdrawn by subject	4
Adverse event, non-fatal	1
Lung transplant	1
Travel/vacation	1
Drug abuse	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	140	140	
Age categorical			
Units: Subjects			
Adults (18-64 years)	130	130	
From 65-84 years	10	10	
Gender categorical			
Units: Subjects			
Female	61	61	
Male	79	79	

End points

End points reporting groups

Reporting group title	Zemaira®
Reporting group description: -	
Subject analysis set title	Zemaira® (Early Start)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Those subjects who had already been allocated to receive Zemaira® treatment during study CE1226_4001 represent the Early Start group. This group had received up to 4 years of continuous therapy at the end of study CE1226_3001. The subjects in this group were from the Intention-to-treat population. Subjects may not have been included in all efficacy analyses because of missing efficacy assessments.

Subject analysis set title	Zemaira® (Delayed Start)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received placebo in study CE1226_4001 and only began to receive Zemaira® treatment upon entry into study CE1226_3001 represent the Delayed Start group. This group had a maximal exposure of 2 years at the end of study CE1226_3001. The subjects in this group were from the Intention-to-treat population. Subjects may not have been included in all efficacy analyses because of missing efficacy assessments.

Primary: Rate of change of adjusted lung density

End point title	Rate of change of adjusted lung density
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End point description:

As measured by centralized, standardized computer tomographic (CT) lung densitometry. CT scans were acquired at 2 inspiration states: TLC (Total Lung Capacity; ie, full inspiration) and FRC (Functional Residual Capacity; ie, full expiration). Results were adjusted for total lung volume and are presented as point estimates for the average rate of decline in the early start and delayed start subgroups from a linear random regression model with country, inspiration state (only for 'TLC and FRC state'), time (time elapsed since Day 1 [CE1226_4001]), treatment and treatment by time interaction as fixed effects and subject and subject by time interaction as random coefficients.

End point type	Primary
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End point timeframe:

Up to 2 years

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	64		
Units: g/L per year				
least squares mean (standard error)				
TLC + FRC combined	-1.632 (± 0.2824)	-1.352 (± 0.2961)		
TLC	-1.627 (± 0.2743)	-1.256 (± 0.2891)		
FRC	-1.658 (± 0.3186)	-1.482 (± 0.3346)		

Statistical analyses

Statistical analysis title	TLC and FRC combined
Statistical analysis description:	
Analysis of the annual rate of change in lung density (for TLC + FRC combined) was a linear random regression model with country, inspiration state, time since Day 1 [CE1226_4001], and treatment-by-time interaction as fixed effects and subject and subject-by-time interaction as random coefficients at a 1-sided significance level of 0.025.	
Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.752 ^[1]
Method	Regression, Linear
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	-0.279
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.089
upper limit	0.53

Notes:

[1] - A 1-sided P-value < 0.025 and a positive estimate of the treatment difference Early Start minus Delayed Start (ie, the lower bound of the 95% confidence interval [CI] being > zero) will indicate superiority of Early Start compared with Delayed Start.

Statistical analysis title	TLC
Statistical analysis description:	
Analysis of the annual rate of change in lung density (for TLC) was a linear random regression model with country, time since Day 1 [CE1226_4001], and treatment-by-time interaction as fixed effects and subject and subject-by-time interaction as random coefficients at a 1-sided significance level of 0.025.	
Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.823 ^[2]
Method	Regression, Linear
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	-0.371
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.159
upper limit	0.417

Notes:

[2] - A 1-sided P-value < 0.025 and a positive estimate of the treatment difference Early Start minus Delayed Start (ie, the lower bound of the 95% CI being > zero) will indicate superiority of Early Start compared with Delayed Start.

Statistical analysis title	FRC
Statistical analysis description:	
Analysis of the annual rate of change in lung density (for FRC) was a linear random regression model with country, time since Day 1 [CE1226_4001], and treatment-by-time interaction as fixed effects and subject and subject-by-time interaction as random coefficients at a 1-sided significance level of 0.025.	
Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.648 ^[3]
Method	Regression, Linear
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	-0.176
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	0.738

Notes:

[3] - A 1-sided P-value < 0.025 and a positive estimate of the treatment difference Early Start minus Delayed Start (ie, the lower bound of the 95% CI being > zero) will indicate superiority of Early Start compared with Delayed Start.

Secondary: Absolute change in adjusted lung density

End point title	Absolute change in adjusted lung density
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End point description:

Absolute change from baseline to 2 years as measured by centralized, standardized CT lung densitometry. CT scans were acquired at 2 inspiration states: TLC (ie, full inspiration) and FRC (ie, full expiration). Results were adjusted for total lung volume and are presented as point estimates for the average absolute change in the early start and delayed start subgroups from an analysis of covariance (ANCOVA) model with country, treatment, and baseline lung density as fixed effects and inspiration state as a repeated random effect. The baseline is the last assessment from the preceding study CE1226_4001.

End point type	Secondary
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End point timeframe:

From baseline to 2 years

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	60		
Units: g/L				
least squares mean (standard error)				
TLC and FRC combined, n = 64, 60	-3.031 (± 0.5888)	-2.502 (± 0.6142)		
TLC, n = 64, 59	-2.971 (± 0.5826)	-2.485 (± 0.6142)		
FRC, n = 64, 60	-2.934 (± 0.6671)	-2.953 (± 0.6993)		

Statistical analyses

Statistical analysis title	TLC + FRC combined
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Statistical analysis description:

Analysis of the change in lung density (for TLC + FRC combined) from baseline to 2 years was analyzed using an ANCOVA model with country, treatment, and baseline lung density as fixed effects and inspiration state as a repeated random effect.

Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.526 ^[4]
Method	ANCOVA
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.179
upper limit	1.12

Notes:

[4] - Two-sided P-value

Statistical analysis title	TLC
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Statistical analysis description:

Analysis of the change in lung density (for TLC) from baseline to 2 years was analyzed using an ANCOVA model with country, treatment, and baseline lung density as fixed effects.

Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.558 ^[5]
Method	ANCOVA
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	-0.486
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.126
upper limit	1.154

Notes:

[5] - Two-sided P-value

Statistical analysis title	FRC
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Statistical analysis description:

Analysis of the change in lung density (for FRC) from baseline to 2 years was analyzed using an ANCOVA model with country, treatment, and baseline lung density as fixed effects.

Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.984 ^[6]
Method	ANCOVA
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	0.019

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.858
upper limit	1.895

Notes:

[6] - Two-sided P-value

Secondary: Percent change in adjusted lung density

End point title	Percent change in adjusted lung density
End point description:	
Percent change from baseline to 2 years as measured by centralized, standardized CT lung densitometry. CT scans were acquired at 2 inspiration states: TLC (ie, full inspiration) and FRC (ie, full expiration). Results were adjusted for total lung volume and are presented as point estimates for the average percent change in the early start and delayed start subgroups from an ANCOVA model with country, treatment, and baseline lung density as fixed effects and inspiration state as a repeated random effect. The baseline is the last assessment from the preceding study CE1226_4001.	
End point type	Secondary
End point timeframe:	
From baseline to 2 years	

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	60		
Units: Percent change from baseline				
least squares mean (standard error)				
TLC and FRC combined, n = 64, 60	-6.741 (± 1.4031)	-7.035 (± 1.4671)		
TLC, n = 64, 59	-6.825 (± 1.4286)	-6.674 (± 1.5061)		
FRC, n = 64, 60	-6.494 (± 1.5027)	-8.281 (± 1.5752)		

Statistical analyses

Statistical analysis title	TLC and FRC combined
Statistical analysis description:	
Analysis of the percent change in lung density (for TLC + FRC combined) from baseline to 2 years was analyzed using an ANCOVA model with country, treatment, and baseline lung density as fixed effects and inspiration state as a repeated random effect.	
Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.883 ^[7]
Method	ANCOVA
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	0.294

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.645
upper limit	4.233

Notes:

[7] - Two-sided P-value

Statistical analysis title	TLC
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Statistical analysis description:

Analysis of the percent change in lung density (for TLC) from baseline to 2 years was analyzed using an ANCOVA model with country, treatment, and baseline lung density as fixed effects.

Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.941 ^[8]
Method	ANCOVA
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	-0.151

Confidence interval

level	95 %
sides	2-sided
lower limit	-4.172
upper limit	3.87

Notes:

[8] - Two-sided P-value

Statistical analysis title	FRC
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Statistical analysis description:

Analysis of the percent change in lung density (for FRC) from baseline to 2 years was analyzed using an ANCOVA model with country, treatment, and baseline lung density as fixed effects.

Comparison groups	Zemaira® (Early Start) v Zemaira® (Delayed Start)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.404 ^[9]
Method	ANCOVA
Parameter estimate	Difference in lung density(adjusted P15)
Point estimate	1.787

Confidence interval

level	95 %
sides	2-sided
lower limit	-2.44
upper limit	6.014

Notes:

[9] - Two-sided P-value

Secondary: Change in subject-reported symptoms

End point title	Change in subject-reported symptoms
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End point description:

Patient-reported symptoms were measured using the St George's Respiratory Questionnaire (SGRQ). SGRQ total, symptoms, activity and impact scores range from 0 to 100, with higher scores indicating more limitations, and change from baseline below zero (0) is favorable, indicating improvement.

End point type	Secondary
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End point timeframe:

From baseline to 2 years

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67	58		
Units: Units on a scale (change from baseline)				
arithmetic mean (standard deviation)				
Total score, n = 62, 56	1.185 (± 13.624)	1.499 (± 12.0507)		
Symptoms score, n = 67, 58	6.601 (± 22.29)	0.728 (± 19.2189)		
Activity score, n = 67, 57	0.55 (± 14.1429)	2.831 (± 14.0013)		
Impact score, n = 65, 57	-0.22 (± 15.8999)	1.626 (± 13.5699)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in lung function as measured by forced expiratory volume in 1 second (FEV1)

End point title	Percent change in lung function as measured by forced expiratory volume in 1 second (FEV1)
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End point description:

End point type	Secondary
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End point timeframe:

From baseline up to 2 years

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	69	56		
Units: Percent change from baseline				
arithmetic mean (standard deviation)	-8.61 (± 12.9541)	-8.666 (± 10.9057)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in lung function as measured by ratio of FEV1/FVC (forced vital capacity)

End point title	Percent change in lung function as measured by ratio of FEV1/FVC (forced vital capacity)
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End point description:

End point type	Secondary
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End point timeframe:

From baseline up to 2 years

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	69	56		
Units: Percent change from baseline				
arithmetic mean (standard deviation)	0.56 (± 12.9685)	-5.441 (± 10.8993)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in lung function as measured by percent predicted FEV1

End point title	Percent change in lung function as measured by percent predicted FEV1
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End point description:

End point type	Secondary
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End point timeframe:

From baseline up to 2 years

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	54		
Units: Percent change from baseline				
arithmetic mean (standard deviation)	-7.165 (± 13.2053)	-6.958 (± 11.0846)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with pulmonary exacerbations

End point title	Number of subjects with pulmonary exacerbations
End point description:	
End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	64		
Units: Subjects				
No exacerbation	13	16		
Overall (at least 1 exacerbation)	63	48		
Moderate exacerbation	60	46		
Severe exacerbation	17	11		
Neither moderate or severe exacerbation	21	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual rate in subject years of pulmonary exacerbations

End point title	Annual rate in subject years of pulmonary exacerbations
End point description:	
Annual exposureadjusted incidence rate of pulmonary exacerbations.	
End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	64		
Units: Exacerbations/subject year				
number (confidence interval 95%)	1.71 (1.49 to 1.92)	1.39 (1.18 to 1.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first pulmonary exacerbation

End point title	Time to first pulmonary exacerbation
End point description:	
End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	64		
Units: years				
median (confidence interval 95%)	0.405 (0.315 to 0.687)	0.602 (0.287 to 0.843)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment Emergent Adverse Events

End point title	Percentage of Subjects With Treatment Emergent Adverse Events
End point description:	
Percentage of subjects with treatment-emergent adverse events (TEAEs): overall, by severity, by relatedness, by seriousness, and which occurred within 24 hours of Zemaira® administration.	
End point type	Secondary
End point timeframe:	
From baseline up to 2.5 years	

End point values	Zemaira® (Early Start)	Zemaira® (Delayed Start)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	64		
Units: Percentage of subjects				
number (not applicable)				
Any TEAE	100	96.9		
Mild TEAE	19.7	15.6		
Moderate TEAE	50	51.6		
Severe TEAE	30.3	29.7		
Any related TEAE	14.5	10.9		
Any serious TEAE	36.8	35.9		
Any TEAE within 24 hrs	86.8	79.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 2.5 years

Adverse event reporting additional description:

Treatment-emergent adverse events are presented.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Zemaira®
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Reporting group description:

The safety population comprised all subjects enrolled in study CE1226_3001 and who received at least 1 administration of Zemaira® during study CE1226_3001.

Serious adverse events	Zemaira®		
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 140 (36.43%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hysterectomy			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung transplant			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Strangulated hernia repair			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			

subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral thrombosis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotonia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar radiculopathy			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	3 / 140 (2.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal wall haematoma				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	17 / 140 (12.14%)		
occurrences causally related to treatment / all	0 / 43		
deaths causally related to treatment / all	0 / 1		
Pneumothorax			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchiectasis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nocturnal dyspnoea			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary fibrosis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 140 (4.29%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	4 / 140 (2.86%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Herpes zoster			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Zemaira®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 140 (97.86%)		
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 140 (20.00%)		
occurrences (all)	58		
General disorders and administration			

site conditions Condition aggravated subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	27 / 140 (19.29%) 71 12 / 140 (8.57%) 13 10 / 140 (7.14%) 15		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	11 / 140 (7.86%) 11 10 / 140 (7.14%) 11		
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	50 / 140 (35.71%) 137 19 / 140 (13.57%) 21 17 / 140 (12.14%) 40 15 / 140 (10.71%) 27		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	15 / 140 (10.71%) 19		
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	40 / 140 (28.57%)		
occurrences (all)	72		
Lower respiratory tract infection			
subjects affected / exposed	20 / 140 (14.29%)		
occurrences (all)	106		
Upper respiratory tract infection			
subjects affected / exposed	16 / 140 (11.43%)		
occurrences (all)	37		
Influenza			
subjects affected / exposed	15 / 140 (10.71%)		
occurrences (all)	17		
Oral candidiasis			
subjects affected / exposed	13 / 140 (9.29%)		
occurrences (all)	37		
Bronchitis			
subjects affected / exposed	12 / 140 (8.57%)		
occurrences (all)	22		
Pneumonia			
subjects affected / exposed	10 / 140 (7.14%)		
occurrences (all)	17		
Sinusitis			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences (all)	15		
Urinary tract infection			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2008	Protocol version 2 harmonized the statistical analysis methods to match those foreseen for study CE1226_4001 and introduced a more detailed efficacy analysis.
15 May 2013	Protocol version 4 reflects changes to the statistical analysis plan for study CE1226_3001 following the corroboration of study CE1226_4001 data with the EXACTLE results (Dirksen et al 2009). An interim analysis was added to study CE1226_3001 to occur 2 years prior to study completion, to assess the disease-modifying potential over 4 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported